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Biologic and Clinical Significance of CD7 Expression in Acute Myeloid Leukemia

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CD7 antigen, a T-cell lineage associated antigen, is expressed in a minority of patients with acute myeloid leukemia (AML). The biologic and clinical significance of this finding is not clearly established. In this retrospective study of patients with de novo acute myeloid leukemia, we have identified CD7 expression and analyzed its association with markers expressed early in hemopoietic ontogeny and clinical parameters. Among 60 consecutive AML patients, we found six (10%) expressing CD7 on leukemic cells. There were five males and one female and the mean age was 59.6 years (age range: 32–76 years) with no demographic peculiarities. The FAB subtypes were: M0 (2), M1 (1), M2 (1), and M4 (2). CD7 expression was associated with immature antigens CD34, HLA-DR, and terminal deoxynucleotidyl transferase (TdT) and antigen receptor gene rearrangements (rearrangements of T-cell receptor gamma chain in 6/6 and immunoglobulin heavy chain in 2/6). Hepatomegaly was present in three and this was associated with splenomegaly with lymphadenopathy in one patient. Mediastinal or central nervous system involvement was absent. Complete remission was achieved in two patients with standard chemotherapy; one of these is in remission and alive (5 years later), while one died following relapse 9 months later. Three patients had significantly lower response to standard therapeutic regimen (two died during induction and one died 7 months later without ever achieving complete remission). One patient has been excluded in determining the prognostic significance of CD7 due to early death. Our results suggest origin of CD7+ AML from early hemopoietic precursors and indicate biologic aggressiveness in a significant proportion of patients. We suggest evaluation of CD7 in all patients with AML at the time of diagnosis in view of poor clinical outcome. Am. J. Hematol. 58:278–284, 1998.

Key words: acute myeloid leukemia; CD7 antigen; immunophenotyping; antigen receptor gene rearrangements; prognosis; biologic significance

INTRODUCTION

Flow cytometric characterization of hematopoietic neoplasms using monoclonal antibodies against lineage and differentiation markers [1,2] has helped in more precise and objective classification of these malignancies. Immunophenotyping has also highlighted ''aberrant'' antigen expression [3,4], e.g., CD2 [5] expression in acute myeloid leukemia. One of the T-cell lineage markers, CD7, has been detected on the leukemic cells in a minority of AML cases [6–9]. The significance of this finding is not clearly established. Biologically, it could represent aberrant lymphoid antigen expression on myeloid blasts or maybe a marker of a developmental stage in myelopoiesis. The latter is a likely possibility in view of the association of CD7 expression with terminal deoxynucleotidyl transferase (TdT) [10] and other immature markers, e.g., CD34 and HLA-DR. The clinical features of patients with CD7+ AML are not uniform. CD7 has been reported to be associated with a constellation of clinical findings (young males, hepatosplenomegaly, central nervous system involvement) [11] while other studies have failed to confirm this [8,12]. Although immunophenotypic findings are not a major determinant of

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TABLE I. Clinical Features of CD7+ AML*

Case	Age/sex	Liver/LN	spleen	CNS/med. disease	Chemo-response	therapy	Outcome
1	57/M	+/−	−	−	I, A	−	Death, D 21
2	54/M	−/−	−	−	I,A,H	Pri. resistant	Death D 230
3	72/F	−[a]/−	−	−	I, A	CR	Relapse D 240, Death D 395
4	32/M	−/−	−	−	I, A	CR	Alive, R, 5 yrs.
5	76/M	+/−	−	−	I, A	−	Death D 28
6	67/M	+/+	+	−	I, A	−	Death D 2

*A, cytosine arabinoside; CR, complete remission; H, hydroxyurea; I, idarubicin; R, in remission; death D, death on day; LN, lymphadenopathy; CNS/med. disease, central nervous system or mediastinal disease.
[a]There were transient liver lesions detected by ultrasound examination, which disappeared before fine-needle aspiration could be arranged, and were believed to represent cholestatic liver disease secondary to chemotherapy.

prognosis compared to cytogenetic abnormalities [13], expression of CD7 in association with ''immature antigens'' has prompted studies to evaluate its effect on clinical course and treatment response. The effect on prognosis is controversial, with reports of adverse prognosis [11,12,14,15], no effect on prognosis [16,17], and favorable prognosis [18]. To address the biologic and clinical significance of CD7 expression in AML, we have retrospectively analyzed 60 consecutive cases of de novo AML for CD7 expression and correlated this with French American British (FAB) classification of AML, expression of other ''immature'' antigens, antigen receptor gene rearrangements, clinical findings, and prognosis. CD7 was detected in leukemic cells in six patients (10%) and correlated with expression of CD34, TdT, HLA-DR, antigen receptor gene rearrangement in six patients, and poor response to treatment and adverse prognosis in five patients.

MATERIALS AND METHODS

Patients

Sixty consecutive adult patients with de novo AML over a 4-year period (1993–1996) seen at Royal University Hospital were retrospectively analyzed. Clinical data were obtained from patient records in Saskatoon Cancer Clinic and the records in Pathology archives. Six AML patients with expression of CD7 on myeloid blasts were found and these form the basis of this report.

Morphology and Cytochemistry

Wright-Giemsa stained marrow aspirates and cytochemical stains were evaluated according to the FAB criteria [2,19]. The presence of terminal deoxynucleotidyl transferase (TdT) was determined by indirect immunoflourescence.

Immunophenotyping

Data generated from the flow cytometric analysis performed for diagnostic workup was evaluated for antigen expression. Briefly, total leukocyte and differential counts were performed on all bone marrow and peripheral blood samples and the sample cell count was adjusted to 5–10 × 10^6 ml. One hundred microliters of this suspension was incubated with 50μl of antibody reagent mixture for 20 min at room temperature, followed by lysis using the 35-sec setting on the Q-prep. Cell surface markers were analyzed using antibodies against CD45, CD34, CD13, CD33, CD15, CD11b, CD14, HLA-DR, CD2, CD7, CD19, CD20, CD41, CD61, and Glycophorin. Fluorescein-conjugated goat anti-mouse Ig (GAM-FITC) was used as the secondary antibody. All samples were analyzed on the day of collection in an EPICS-Profile II flow cytometer at 488 nm. Cells were gated by light scatter and ''blast'' fraction was further analyzed [20]. Due to extremely low background of the anti-CD7 reagents on AML cells, its expression was considered positive when more than 20% of leukemic cells stained with this antibody.

Antigen Receptor Gene Rearrangements

DNA was extracted from bone marrow aspirates and/or core biopsies by the QIAmp blood/tissue kit (Qiagen; Santa Clarita, CA) and amplified with PCR using standard protocol. Gene rearrangements were detected using primers directed against the J region (5′-ACCTGAGGAGACGGTGACC-3′) and the V region (5′-CTGTCGACACGGC (C/T)(G/C)TGTATTACTGT-3′) of the immunoglobulin heavy chain gene, and the J region (5′-CCCGTCGACTACCTTGGAAATGTTGTATTCTTC-3′) and the V region (TACATCCACTGGTACCTACACCA-3′) of the T-cell receptor gamma gene. The PCR products were visualized on 1% agarose gel and the MDE polyacrylamide gel, respectively, stained with ethidium bromide, and photographed under ultraviolet light.

RESULTS

Clinical Features

The clinical features are summarized in Table I. The age range was 32–76 years (mean age: 59.6 years). The

TABLE II. Cell Counts at Presentation, Morphologic and Cytochemical Findings, and CD7 Expression in CD7+ AML*

						MPO NSE		
Case no.	WBC	Hb	Platelets	Circulating blasts (%)	FAB type	% pos.	% pos.	CD7 (% pos.)
1	9.6	82	78	45	M4	70	25	44.5
2	93.4	126	94	68	M0	−ve	−ve	72.0
3	93	77	54	36	M0	<3	−ve	48.9
4	3.6	52	36	42	M4	60	25	72.5
5	13.1	101	12	62	M2	98	0	76.4
6	343	83	54	90	M1	95	0	31.6

*WBC, ($\times 10^{-9}$/L); Hb, (g/L); Platelets, ($\times 10^{-9}$/L); MPO, myeloperoxidase (percent of positive blasts in the bone marrow); NSE, non-specific esterase (percent of positive nonerythroid cells in the bone marrow).

TABLE III. Immunophenotype of CD7+ AML With Corresponding FAB Subtypes

Case	FAB	CD34	CD33	CD13	CD2	CD7	CD14	CD11b	HLA-DR
1	M4	75.3	40.6	62.6	11.8	44.5	9.1	13.1	70.6
2	M0	74.4	79.0	79.5	3.5	72.0	15.3	26.6	90.3
3	M0	69.1	42.5	7.0	15.0	48.9	12.1	19.0	92.1
4	M4	88.4	44.5	14.4	16.5	70.5	35.1	72.0	87.8
5	M2	84.2	52.1	70.4	15.0	76.4	<2.0	5.5	9.0
6	M1	71.2	96.1	72.8	2.4	31.6	<2.0	5.6	61.8

male:female ratio was 5:1. Three patients had hepatomegaly and in one it was associated with splenomegaly and lymphadenopathy. None had mediastinal or central nervous system involvement. All patients were treated with standard AML protocol. One patient (case 6) had early death (death within 2 weeks). Three patients responded unfavorably to induction therapy; one (case 2) was primary resistant and two (cases 1 and 5) died at days 21 and 28, respectively. Although complete remission was achieved in two patients (cases 3 and 4), one (case 3) died following relapse and only one is alive and continues to be in remission after 5 years (case 4). The difference in complete remission induction between CD7+ patients (2/6) and CD7-patients (46/54) is statistically significant (Fisher's exact test, $P = 0.012$).

Blood Counts, Morphologic and Cytochemical Findings

These findings are shown in Table II. The leukocyte count at the time of diagnosis ranged from 3.6–343 $\times$ 10^9/L. Circulating blasts were present in all patients (36–90%). The FAB subtypes were M1 (case 6), M2 (case 5), and M4 (cases 1 and 4) with typical myeloperoxidase and non-specific esterase cytochemical reaction patterns. Two cases (cases 2 and 3) were considered M0 acute leukemia (myeloperoxidase negative and <3%, respectively, by cytochemistry) in view of myeloid antigen (CD13 and 33) expression coupled with absence of B- and T-cell lineage markers. Alternatively, these two cases could be examples of mixed lineage leukemia. TdT was present in all six cases.

Immunophenotype of CD7+ AML

The immunophenotypic findings of the ''blast region'' gated by light scatter are depicted in Table III. CD7+ cases had a well-defined peak of positive cells while CD7-cells had fluorescence curves overlapping the negative controls (Fig. 1). The blasts exhibited characteristic AML antigen profile with expression of CD13 and CD33. Expression of monocytoid antigens CD14 and CD11b was variable. HLA-DR, the other myeloid progenitor antigen, was observed in all cases. However, its expression was low in case 5. Expression of CD34 and HLA-DR as well as coexpression of these two antigens as determined by marked overlap of cells expressing each antigen was more common in CD7+ AML compared to CD7-AML ($P < 0.1$), data not shown.

Gene Rearrangement Studies

Antigen receptor rearrangements are shown in Figure 2. T-cell receptor gene rearrangement as determined by PCR using gamma chain primers was found in all six cases. Biallelic rearrangement was detected in one case (case 3). Immunoglobulin heavy chain gene was rearranged in two cases (cases 2 and 3, both FAB-MO).

DISCUSSION

In this study we describe the biologic and clinical importance of CD7 expression in AML. Expression of ''immature'' markers, CD34, HLA-DR, TdT, coupled with minimal differentiation in two cases (FAB subtype MO

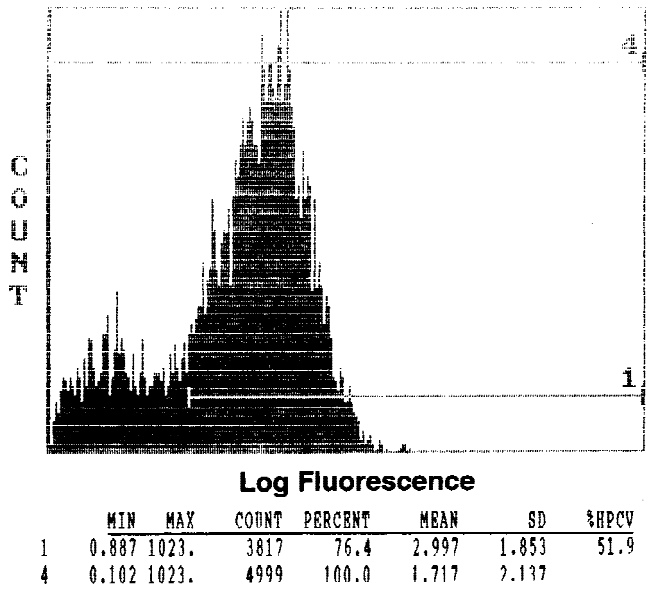

Fig. 1. CD7 expression on myeloid blasts. Single parameter histogram of CD7+ cells from patient 5; CD7+ population (44.5%) is clearly distinct from background (counts on Y axis and log fluorescence on X axis).

or mixed lineage acute leukemia) and the presence of antigen receptor gene rearrangements, point toward an earlier ''stem'' cell origin of CD7+ AML. One patient out of six (case 6) experienced early death (death within 2 weeks) and has been excluded in determining the clinical importance of CD7 expression. Of the remaining five, only one patient continues to be in remission, while most of the patients (4/5) exhibited poor response to standard chemotherapy and had an unfavorable outcome.

The patients investigated in this study had classical AML phenotypes along with solitary CD7 expression without any tendency for one phenotype to predominate (MO/mixed lineage, M1, M2, and M4). CD7, likely a receptor for IgM Fc fragment [21], is a T-cell associated antigen expressed on immature thymocytes, mature T-cells, and T-cell malignancies [22,23].

Biologic Significance

CD7 expression has been reported in from 10% to more than 30% of AML cases [8,9,11,12,14], frequently in association with ''immature'' markers such as CD34, TdT, and HLA-DR. Our study has confirmed the association with CD34, HLA-DR, and TdT. About 5–10% of AML cases with expression of T-cell antigens including CD7 have concomitant rearrangements in the immunoglobulin heavy chain and T-cell receptor beta and gamma genes [6–9], while solitary CD7 expression in AML correlates with higher TCR delta and TCR beta rearrangements in a majority of patients [14]. In T-cell ontogeny, the sequence of rearrangement of different TCR genes is: delta, gamma, beta, and alpha [24,25]. We analyzed TCR gamma gene due to the following reasons (1) it is the most frequently arranged gene in T-cell malignancies and has been shown to be the most informative and early marker of clonality in T-cell malignancies [26]; (2) only a few V-J specific primers are required (4 V and 3 J) because of a small number of V-J segments and their sequence homology [27,28]; and (3) over 80% of all possible rearrangements can be amplified using a single pair of primers (V1-J1/2) [29,30] because of non-random gene usage [26,31]. The gamma chain was rearranged in all cases and was associated with Ig heavy chain gene rearrangement in two cases, both FAB-MO subtype. Although antigen receptor rearrangements are considered lineage specific, aberrant rearrangements are known to occur in hemopoietic malignancies. The high incidence of antigen receptor gene rearrangements in CD7+ AML in our series is associated with TdT expression. TdT plays an important role in antigen receptor gene rearrangements by inserting nucleotides at VDJ junctions (N regions) in a temple-independent manner, thus contributing to antigen receptor diversity [32,33].

Expression of TdT, CD7, and antigen receptor gene rearrangements are early events in lymphoid development [25] while CD34 and HLA-DR expression are early events in myelopoiesis [34]. The coexistence of these ''early'' markers in a subset of AML may be a chance phenomenon. However, this seems unlikely in view of the constant association of the majority of these events in CD7+ AML. It has been postulated that TdT expression and antigen receptor gene rearrangement(s) may be a normal and early differentiation step in hemopoiesis prior to myeloid lineage committment (lineage promiscuity) [35] and detection of these in AML could be ''footprints'' of this phenomenon [10]. Some of the CD7+ AML may arise from clonal expansion of these cells. The association of CD7 with immature precursors is further supported by in vitro demonstration of myeloid potential of CD34+CD7+ human marrow cells [36] and of immature thymocytes [37] and its expression on fetal liver precursor cells [25]. In addition, CD3 transcripts, another early T-lineage characteristic, have been demonstrated in myeloid blasts [15].

Based on our findings, we agree with other investigators [6,9,38] that in CD7+ AML, malignant transformation of a cell placed earlier in ontogeny with variable differentiation potential is a likely event. Hemopoietic cells are dependent upon cytokines for differentiation and proliferation and this is mediated by cytokine receptors that have separate domains for differentiation and proliferation. Mutation at the differentiation site may suppress maturation/differentiation and by stimulating proliferation may contribute to leukemogenesis as has been shown in a myeloid precursor cell line (FDC-P1) in which mutations at tyrosine 807 of the M-CSF receptor abrogate differentiation and promote proliferation [39].

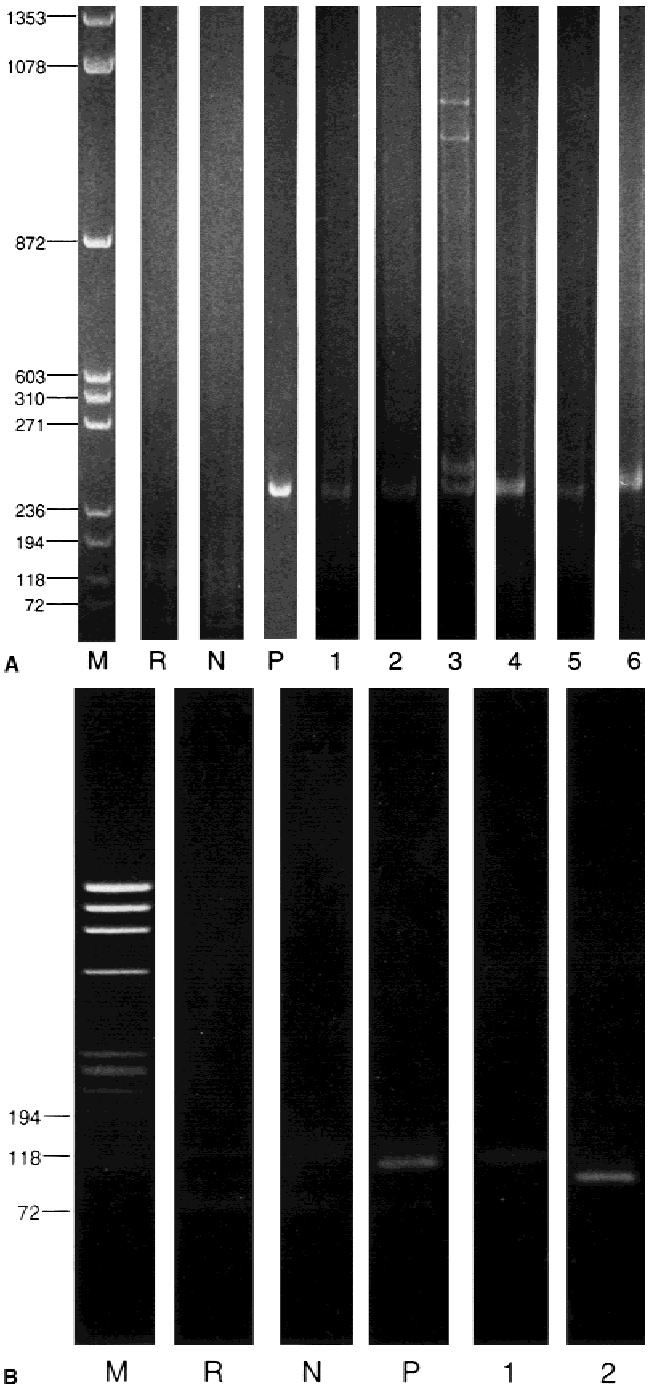

Fig. 2. Gene rearrangements in CD7+ AML. A: Polyacrylamide (MDE) gel electrophoresis of heteroduplex PCR products (V 1 and J 1/2 gamma chain primers) from clinical samples. Lanes: M, molecular weight markers (size in base pairs, bp); R, reagent control; N, negative control; P, positive control; 1–6, corresponding to patient numbers (all cases show clonal bands demonstrating gamma chain gene rearrangement; lane 3 shows biallelic rearrangement demonstrable by homo- and heteroduplexes). B: Ethidium bromide stained agarose gel of FRIII/JH PCR products from DNA samples as follows: Lanes M, molecular weight markers (size in base pairs, bp); R, reagent control; N, negative control, P, positive control; 1 and 2, cases 2 and 3 showing single bands demonstrating Ig heavy chain gene rearrangement.

Clinical Significance

The clinical features associated with CD7 expression are not well established. Similar to our observations, there are other studies in which no restricted age and sex distribution or distinctive clinical presentation was found [8,12]. On the other hand, CD7+ AML patients have been shown to be mainly younger males [11,14], frequently with hepatosplenomegaly and central nervous system involvement [11].

The prognostic value of CD7 expression in AML is uncertain, and the effect on prognosis has been shown to be adverse [11,12,14,15], favorable [18], or no effect [8,16,17,40]. We have observed that CD7+ patients have a lower chance of obtaining first complete remission (CR) (2 out of 5 cases) and have an overall poor prognosis (4 out of 5 cases). The difference in complete remission between CD7+ patients and CD7-patients (46/54) is statistically significant (Fisher's exact test, $P = 0.012$). As CD7 expression in AML is patients with AML at our institution. As CD7 expression in AML is uncommon, a larger number of patients observed over a longer interval is required to address this issue further.

CD7 expression is associated with poor prognosis in T-ALL patients (those with solitary expression of CD7) as well [38] and mediastinal non-Hodgkin's lymphoma [41]. The poor clinical outcome of CD7+ AML patients may be due to the linkage of CD7 expression with a differentiation stage, the function of CD7 molecule, or a mere association with other markers of poor prognosis, e.g., multidrug resistance phenotype (P-170 glycoprotein) [42] and complex karyotypes [43].

Another T-cell related antigen, CD2 has also been shown to be associated with poor prognosis in some studies [11,44]. However, there was coexpression of CD7 and CD2 in these reports, while cases with CD7 expression alone (without CD2) still have poor prognosis [11,12,14,15]. Thus, the diagnostic value of CD7 positivity appears to be superior to CD2.

In conclusion, our study has shown CD7 expression in AML is associated with immature antigens (CD34, HLA-DR, TdT), and antigen receptor gene rearrangements. This is likely to represent an origin from an early stem cell in myeloid development. CD7 expression is also associated with poor clinical outcome (less chance of obtaining first complete remission and overall poor prognosis) in a majority of the patients with AML. Therefore, determining its expression on leukemic cells might be considered a part of immunophenotyping in AML.

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